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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,110	08/31/2001	Andrew C Karaplis	SWA-XXX	5387

7590 12/22/2003
Keown & Associates
500 West Cummings Park
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Woburn, MA 01801

EXAMINER

SHUKLA, RAM R

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 12/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/806,110

Applicant(s)

KARAPLIS ET AL.

Examiner

Ram R. Shukla

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 22 September 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 7-10 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 7-10 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 28 March 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
- a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3/03.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of the invention of claims 7-10 in Paper filed 9-22-2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).
2. Claims 1-6 and 11-19 have been cancelled.
3. Claims 7-10 are pending.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 7-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. When the claims are analyzed in light of the specification, instant invention recites a genus, a modulator of PTH/PTHrP levels. However, the specification does not teach what is the complete structure of any species of the genus. Except for disclosing that an agent or modulator could be any compound, the specification does not teach what would be the structure of a species of the genus.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only identifying characteristic is that the modulator would modulate PTH/PTHrP levels. However, the specification does not disclose any identifying characteristic of such a modulator.

Accordingly, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the applicant is in possession of the broad genus of the modulators or agents at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

6. Claims 7-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claimed invention is broadly drawn to the treatment of any metabolic bone disease by modulating the levels of PTH and/or PTHrP levels in the patient.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any

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necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claimed invention is broadly drawn to the treatment of any metabolic bone disease by modulating the levels of PTH and/or PTHrP levels in the patient. Since the specification teaches cloning of PEX encoding cDNA, it is interpreted as a method of gene therapy using PEX in addition to treatment with any other modulator of PTH/PTHrP.

The specification is not enabling for gene therapy using claimed polynucleotides because the art of gene therapy is highly unpredictable and because the specification does not provide suitable guidance as to how an artisan would have dealt with uncertainties and problems recognized in the art regarding the unpredictability of gene therapy in humans subjects.

In a recent assessment of the gene therapy art, Verma and Somia (Verma IM and Somia N. Nature 389: 239-242. 1997) summarize " In principle, gene therapy is simple: putting corrective genetic material into cells alleviates the symptoms of disease. In practice, considerable obstacles have emerged." They further add " But the problems- such as lack of efficient delivery systems, lack of sustained expression, and host immune response reactions-remain formidable challenges" (see the abstract). Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is no single outcome that we can point to as a success story" (see first and second paragraphs in col 1 on page 239).

Anderson (Anderson WF. Nature 392 (SUPP):25-30, 1998) notes that since the approval of first clinical trial of gene therapy protocol in 1990, more than 300 protocols have been approved worldwide. He further adds, "The

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conclusions from these trials are that gene therapy has the potential for treating a broad array of human diseases and that the procedure appears to carry a very low risk of adverse reactions; the efficiency of gene transfer and expression in human patients is, however, still disappointingly low. Except for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene therapy protocol has been successful in the treatment of a human disease."

Finally, Romano et al (Romano et al. Stem Cells 2000; 18:19-39) reporting on the recent developments of gene therapy, noted, "However, the real effectiveness of gene therapy programs is still in question. After a decade of clinical trials, the therapeutic applications of gene transfer technology are still at a rather preliminary stage."

It is noted that these reviews by the leaders in the field of gene therapy are about those gene therapy protocols and applications where the mechanism of action and some efficacy has been determined in animals models and there may be some extrapolatable correlations indicating the therapeutic effects of a particular gene's encoded protein. Even with such results, it is uncertain whether there would be a therapeutic effect when the studies obtained in a mouse model or another animals model is extended to a human subject.

It is noted that the specification only teaches cloning of PEX cDNA, its characterization, expression pattern in tissues, in vitro translation of PEX cRNA and that the recombinant PEX protein has endopeptidase activity (see pages 9-25 of the specification). The specification does not provide any guidance for teaching any disease with any modulator. The specification does not teach what modulators will be used, how will they be administered, what doses will be used, what type of vectors or delivery vehicles will be used and whether there will be any type of therapeutic effect after the administration of recited modulators. It is noted that the only description regarding any treatment method in the specification is statements such as on

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page 3, lines 25-27 or page 4, lines 18-22. For example, page 4, lines 18-22 of the specification disclose:

"In accordance with the present invention there is provided a method for treatment of metabolic bone diseases comprising administering to a patient a compound for the modulation of PEX enzymatic activity".

Such statements do not provide enabling disclosure since they do not provide any guidance regarding the compound to be used, how will an artisan make such compound and how will an artisan use the compound in treatment of bone disease.

In summary, the specification is not enabling for the claimed invention because the specification does not provide any guidance to practice the claimed treatment methods and an artisan of skill would have undue experimentation to practice the claimed invention since the art of gene therapy in general was unpredictable at the time of the invention and the specification does not provide any teachings for practicing the claimed invention.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 7-10 are rejected under 35 U.S.C. 102(e) as being anticipated by Vickery (US 6,583,114 B2, 6-24-2003, effective filing date 9-9-1997).

Vickery et al teaches healing of fracture healing using PTHrp healing analogs (see the claims and the rest of the patent). It is noted that the claimed invention only teaches step of administering a modulator and therefore, the cited patent anticipates the claimed invention.

9. Claims 7-10 are rejected under 35 U.S.C. 102(e) as being anticipated by Chorev et al (WO 96/19246, 26 June 1996).

The cited art teaches administration of PTH hormone or agonists to human patients for promoting bone formation (see the abstract, claims and rest of the document). It is noted that the claimed invention only teaches step of administering a modulator and therefore, the cited patent anticipates the claimed invention.

10. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for TC 1600 is (703) 703-872-9306. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the William Phillips whose telephone number is (703) 305-3413.

Please note that effective January 13, the offices for Examiner Shukla, SPE Reynolds and LIE William Phillips will move to the new USPTO location in

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Alexandria, VA and their phone numbers will change. The new phone numbers will be as follows:

Ram Shukla: **(571) 272-0735**

Deborah Reynolds: **(571) 272-0734**

William Phillips: **(571) 272-0548**

Ram R. Shukla, Ph.D.
Primary Examiner
Art Unit 1632


RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER